BARNES & THORNBURG

11 South Meridian Street
Indianapolis, Indiana 46204
(317) 236-1313
(317) 231-7433 Fax

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group:	1642
Confirmation No.:	5816
Application No.:	09/822,379
Invention:	**Method of Treatment Using Ligand-Immunogen Conjugates**
Applicant:	Low et al.
Filed:	March 30, 2001
Attorney Docket:	3220-67883
Examiner:	Karen A. Canella

Certificate Under 37 CFR 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450

on 4/22/05

Rebecca Ball
(Signature)

Rebecca L. Ball
(Printed Name)

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. BARTON A. KAMEN

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I declare as follows:

1. I am currently a Professor of Pediatrics and Pharmacology, Director of Pediatric Hematology-Oncology and Associate Director of the Cancer Institute of New Jersey, University of Medicine and Dentistry of New Jersey. I received a Doctorate of Medicine degree and a Doctorate of Philosophy degree (M.D., Ph.D.) from Case Western Reserve University in 1976. My research has focused on folate and anti-folate metabolism/homeostasis and the function(s) of the folate receptor. I have authored or co-authored more than 150 peer-reviewed journal articles and more than 60 book chapters in the area of my research interests. A copy of my curriculum vitae is attached as Exhibit A.

2. I have read and understand the specification of the captioned application and the pending claims in the application. The pending claims of the captioned patent application are directed to methods and compositions for enhancing an endogenous immune response-mediated elimination of a population of cancer cells comprising administering a composition comprising an immunogen conjugated to a folate receptor-binding ligand and a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the conjugate.

3. An exemplary *in vivo* experiment using the claimed method is shown in Fig. 1 below. Mice (n = 8 mice/group) were preimmunized with an immunogen and were subsequently injected with M109 cancer cells using an intraperitoneal tumor model. The mice were then injected with a conjugate comprising the immunogen linked to a folate receptor-binding ligand. Control mice were injected with PBS. One group of control mice and one group of the mice treated with the conjugate were then treated with cytokines, compounds capable of stimulating an endogenous immune response. The specific method used is described in detail in Example 7 on page 22 of the patent application. Fig. 1 below is analogous to Fig. 7 in the patent application. The results shown in Fig. 1 below demonstrate that the capacity of a folate-immunogen conjugate to promote long-term survival of tumor-bearing mice is strongly synergistic with cytokines, the cytokines alone having a negligible effect on the survival of the mice in the absence of the folate-immunogen conjugate and the folate-immunogen conjugate alone having only a minor effect.

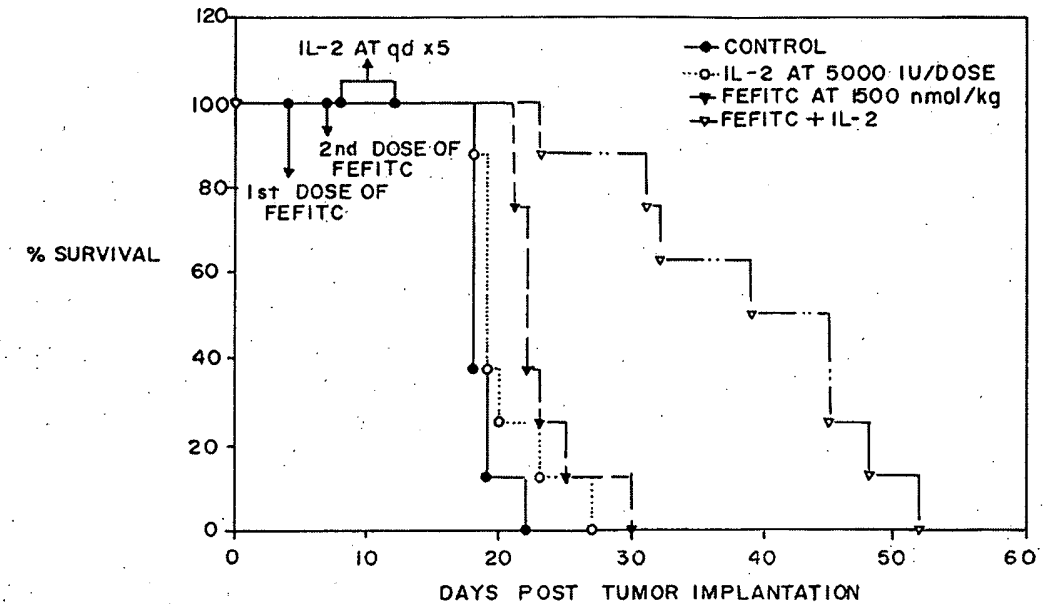
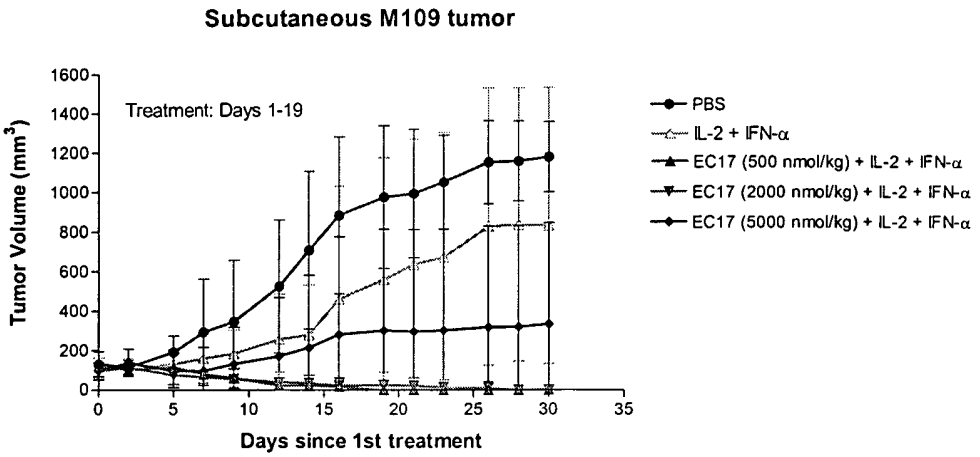


FIG. 1

4. I understand that the licensee of the captioned application is now in Phase I clinical trials with the method described and claimed in the present application as a cancer therapy. I understand that *in vivo* assays have been performed by Dr. Yingjuan Lu, a listed inventor on the captioned application and a research scientist for the licensee, for submission to the FDA in Investigational New Drug Study Reports. These assays utilized an M109 subcutaneous tumor model in Balb/c mice, and compared the effect on tumor volume (mm^3) of a folate-immunogen conjugate (EC17) in combination with cytokines with the effect on tumor volume of cytokines alone. Control mice were injected with PBS. Exemplary data (n = 8 mice/group) generated in such an assay are shown below in Fig. 2. I have studied the data shown in Fig. 2. Tumors were implanted 10 days before treatments were initiated (treatments were initiated on day 1 as shown in Fig. 2).



EC17 and IL-2 (20,000 IU/day) were s.c. dosed at 5 times/week for 3 weeks;
IFN-α (25,000 U/day) was s.c. dosed at 3 times/week for 3-weeks; N = 8

FIG. 2

5. The data in Fig. 2 show that in animals treated with the compositions and methods described and claimed in the present application, a complete response (*i.e.*, disappearance of the tumor) was observed in up to 100% of the mice. In contrast, in animals treated with cytokines alone, a maximum response of only 25% was observed. I also understand that *in vivo* assays have been performed by Dr. Yingjuan Lu which utilized the same tumor model as used for the assay shown in Fig. 2 and the maximum response observed with EC17 alone was 37.5%.

6. I understand that in the assay shown in Fig. 2, some of the mice that showed a complete response, in the groups treated with EC17 and cytokines, were subsequently used in other assays. All of the remaining mice that showed a complete response, in the groups treated with EC17 and cytokines, were left untreated for a period of 11 months following tumor implantation and no recurrence of disease was observed. These mice were sacrificed after 11 months to make room for other animals in the animal facility.

7. I understand that the effect (*i.e.*, complete tumor disappearance in up to 100% of mice) demonstrated in Fig. 2 is being consistently obtained. These results demonstrate that a complete response (*i.e.*, complete disappearance of tumors) can be obtained in mice with

solid tumors that are treated with folate-immunogen conjugates in combination with cytokines. Cyokines and folate-immunogen conjugates alone each have a considerably reduced effect. A complete response (*i.e.*, complete tumor disappearance) is an unexpected result in the field of cancer therapies utilizing combinations of cancer drugs, particularly where the drugs have never been previously combined.

All statements herein made of my own knowledge are true, and all statements herein made on information and belief are believed to be true; these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Dated:

4/13/05

By:

Barton A. Kamen, M.D., Ph.D.